Assessment of Holter ST monitoring for risk stratification in patients with acute myocardial infarction treated by thrombolysis

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Abstract

***Objectives*—To evaluate the role of Holter ST monitoring for identifying patients at risk of recurrent ischaemic events after acute myocardial infarction treated by thrombolysis.**

***Background*—The natural history of myocardial infarction has changed with the introduction of thrombolytic treatment. There is now a lower mortality but a higher incidence of recurrent thrombotic events (reinfarction, unstable angina). Preliminary evidence indicates that Holter ST monitoring may be of prognostic value in patients with acute myocardial infarction, but there are limited data available in patients treated by thrombolysis.**

***Methods*—Prospective observational study of 256 consecutive patients who presented with acute myocardial infarction treated by thrombolysis. All underwent 48 hour Holter ST monitoring early after thrombolysis (mean 83, range 48–180 hours) and were followed up for eight (range three to 12) months.**

***Results*—Recurrent ischaemic events occurred in 45 patients (fatal reinfarction 17, non-fatal reinfarction 12, unstable angina 16). Also four patients died as a result of progressive heart failure, and a further 15 patients required revascularisation. Analysis of the Holter data showed that 32% of patients had at least one episode of isolated ST depression ($\geqslant 0 \cdot 1$ mV) and 41% either ST depression or elevation ($\geqslant 0 \cdot 2$ mV). Ischaemic episodes were silent in 95% of cases. Event free survival analysis showed a significant association between Holter findings and recurrent ischaemic events (ST depression: $p = 0 \cdot 009$; ST depression or elevation: $p = 0 \cdot 002$). The association remained significant when the end point was restricted to fatal or non-fatal reinfarction (ST depression: $p = 0 \cdot 005$; ST depression or elevation $p = 0 \cdot 001$), the period of greatest risk for patients with an abnormal recording occurred early after investigation. An abnormal Holter recording identified patients at risk of early (within 30 days) reinfarction with 79% sensitivity and 60% specificity. Although positive predictive accuracy was low (11%), a normal Holter recording was associated with 98% negative predictive accuracy.**

***Conclusions*—In patients treated by thrombolysis, ST change on Holter monitoring may be useful for identifying patients at increased risk of recurrent ischaemic events, and in particular early reinfarction.**

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Thrombolytic treatment has favourably influenced the natural history of myocardial infarction by reducing mortality in hospital and during early follow up.[1-3] Despite reductions in mortality, however, the incidence of recurrent thrombotic events (reinfarction, unstable angina) has increased, and there is now an important need for non-invasive tests to identify those patients at greatest risk.[3-8] In the prethrombolytic era, prognosis was largely related to remote ischaemia in patients with multivessel disease or to advanced left ventricular dysfunction. Now, however, many of the recurrent events that occur early after myocardial infarction are the result of coronary reocclusion in patients who have previously been treated successfully by thrombolysis.[9-11]

Since the advent of Holter ST segment monitoring, a considerable amount of information has been obtained that characterises silent ischaemia in patients with chronic stable angina. In these patients, Holter monitoring probably adds little to the prognostic information gained from treadmill stress tests.[12] Much less is known about silent ischaemia in acute coronary syndromes, although preliminary evidence indicates that Holter ST monitoring may be of prognostic value in patients with unstable angina[13-16] and acute myocardial infarction.[17-22] The data for acute myocardial infarction, however, generally antedates the thrombolytic era and may not be relevant to current therapeutic practice. The aim of this prospective study, therefore, was to evaluate the role of Holter ST monitoring for risk stratification after acute myocardial infarction in a large series of patients all of whom received thrombolytic treatment.

Patients and methods

STATISTICAL DETERMINATION OF SAMPLE SIZE

It was decided that for non-invasive tests to be of practical value in risk stratification after infarction, the relation between a positive test should be associated with at least a twofold relative risk for recurrent ischaemic events. The event rate at one year follow up for death or reinfarction was estimated to be 15%-20% based on data from the GISSI, AIMS, TIMI, SWIFT, and Interuniversity Cardiology of the Netherlands trials, and the overall one year event rate with unstable angina included as an end point was therefore estimated to be 25%.[3 4 6-8] It was estimated that, in accordance with previous studies of Holter ST monitoring after acute myocardial infarction, 30% of patients would have a positive test. It was therefore calculated that a sample size of 250 patients would be required to provide 90% power for detecting an association between Holter variables and recurrent ischaemic events assuming a twofold relative risk and a level of significance $\leqslant 0 \cdot 05$.

PATIENT SELECTION

The study group comprised 256 consecutive patients with acute myocardial infarction treated by thrombolysis. The patients were recruited from three separate hospitals in east London. Table 1 shows patient characteristics. The diagnosis of acute myocardial infarction was based on any two of three criteria: typical chest pain, $\geqslant 0 \cdot 1$ mV ST elevation in at least one standard or two precordial leads, rise in serum creatine kinase to >400 IU/l. Most patients (n = 246) were treated with streptokinase (1·5 million IU infused over one hour), and 10 patients received alteplase (100 mg infused over four hours). Specific inclusion criteria were: (a) acute myocardial infarction as defined above; (b) treatment with a thrombolytic agent; (c) uncomplicated course in the coronary care unit without ongoing chest pain, electrical instability, severe heart failure, or need for intravenous treatment 48 hours after completion of thrombolytic treatment; (d) no abnormalities preventing interpretation of ST changes on Holter analysis (left bundle branch block, paced rhythms, digoxin induced ST/T changes).

Table 1 Clinical characteristics of the study group (n = 256)

Characteristics	*Value*
Age (mean (SD, range, yr))	59 11, 33–83
Sex, men (n (%))	222 (87)
Site of infarction (n (%)):	
Anterior	124 (48)
Inferior	132 (52)
Q Wave infarction (n (%)):	
Q wave	208 (81)
Non-Q wave	48 (19)
Killip class (on admission) (n (%)):	
1	180 (70)
2	61 (24)
3	14 (6)
4	1
Time to thrombolysis (mean (SD, range, hours))	4·62 (3·40, 1–24)
Smoking history (n (%)):	
Current	127 (50)
Ex-smoker (>1 month)	58 (22)
Non-smoker	71 (28)
History (n (%)):	
Angina (>1 month)	82 (32)
Previous MI	50 (20)
CABG	6 (2)
Diabetes	26 (10)
Perpheral vascular disease	23 (9)

MI, myocardial infarction; CABG, coronary artery bypass graft.

AMBULATORY ELECTROCARDIOGRAPHIC (HOLTER) MONITORING

Patients underwent 48 hour Holter ST monitoring an average of 83 hours after completion of thrombolytic treatment (range 48–180 hours). All patients were required to be free of chest pain, and to be haemodynamically stable for at least 24 hours before starting Holter monitoring. This was performed with frequency modulated dual channel recorders and high quality pregelled electrodes (Marquette Electronics, Milwaukee, USA). The leads monitored were chosen from a modified precordial lead (V4, V5, V6) and a modified inferior lead (II, III, or aVF) avoiding those with pronounced baseline ST segment abnormalities. Leads with pathological Q waves were avoided where possible. Patients were instructed to keep a simple diary to record episodes of chest pain.

The magnetic tapes (TDK) were analysed with a commercially available computerised system (Marquette Electronics, Milwaukee, USA) after careful manual calibration and review of electrocardiographic complex morphology. Episodes of ST shift were identified on the computer generated trend analysis and validated manually by examination of electrocardiographic strips printed at each point of interest. Examples of baseline traces were also printed and examined at regular intervals during the analysis. All tapes were analysed by a trained investigator (RS) and electrocardiographic traces were reviewed by a second investigator (KR or BM). The tapes were reported prospectively and without knowledge of clinical outcome, recording the number and duration of episodes of ST depression and ST elevation. Significant ST depression was defined as planar or down sloping ST segment shift $\geqslant 0 \cdot 1$ mV in magnitude at 0·08 seconds after the J point that persisted for more than 1 minute. Where there was pre-existing ST depression, $\geqslant 0 \cdot 2$ mV of additional ST depression was regarded as a significant change from baseline. Significant ST elevation was defined as upward shift of the ST segment of $\geqslant 0 \cdot 2$ mV at the J point compared with baseline. Changes in T wave vector were ignored unless accompanied by the ST segment changes described. An interval of more than two minutes was required after the return of the ST segment to baseline before another discrete episode was counted. Each episode was determined to be either symptomatic or silent after review of the patient's angina diary.

MEDICATION

All patients received intravenous heparin (1000 IU/h) started during or immediately after thrombolytic infusion and continued for 24 hours. Also all patients were prescribed aspirin (75–150 mg) daily. Other cardiac medications were prescribed according to the policy of the attending physician. Thus at the time of Holter monitoring, 112 (44%) patients were taking β blockers, 79 (31%) oral nitrates, and 43 (17%) calcium antagonists.

PATIENT FOLLOW UP

All patients were followed up either by telephone interview or formal clinic review, and details of hospital readmissions were then taken from a review of the case notes. The following end points were recorded: fatal and non-fatal myocardial infarction, unstable angina, coronary artery bypass surgery, coronary angioplasty, and cardiac death unassociated with a recurrent ischaemic event. Fatal reinfarction was defined as death associated with confirmed reinfarction or sudden death. The diagnostic criteria for reinfarction were the same as for entry into the study. Unstable angina was defined as prolonged cardiac chest pain associated with acute electrocardiographic changes that required urgent admission to the coronary care unit. For analytical purposes ischaemic events that occurred after revascularisation were not included.

STATISTICAL ANALYSIS

Statistical analysis was undertaken in conjunction with the Epidemiology Research Unit at the London Chest Hospital. All averaged values are expressed as mean (SD). The distribution of discrete variables between groups was compared by the χ^2 test. The clinical value of Holter monitoring was assessed by determining sensitivity, specificity, and positive and negative predictive accuracy. Sensitivity (true positive, divided by true positive plus false negative) is the proportion of patients with a recurrent ischaemic event who are correctly identified by analysis of Holter recording. Specificity (true negative/true negative + false positive) is the proportion of patients without events who are correctly identified by the recording. Positive predictive accuracy (true positive/true positive + false positive) is the proportion of patients with a positive recording who sustain an event. Negative predictive accuracy (true negative/true negative + false negative) is the proportion of patients with a negative recording who do not sustain an event. Cardiac event free probability was estimated by the Kaplan-Meier method[23], and comparison of cardiac event free curves was performed by the log rank test[24] with the EGRET (Epidemiological Graphics, Estimation, and Testing, version 0·26·1) and BMDP (1990 release) statistical software packages.

The study was approved by the Local Ethics Committee, and all patients gave informed written consent.

Results

High quality 48 hour ST recordings were obtained from 250 of the 256 patients enrolled in the study. The recordings were of insufficient quality for reliable ST analysis in the remaining six patients who were therefore excluded from further analysis. There were no recurrent events in five of these patients but one underwent elective coronary artery bypass surgery.

Table 2 Recurrent events (n = 256)

	Recurrent events (n)
Non-fatal reinfarction	12
Fatal reinfarction	17
Unstable angina	16
Death due to CCF	4
Elective CABG	10
Elective PTCA	5

CCF, congestive cardiac failure; CABG, coronary artery bypass graft; PTCA, percutaneous transluminary coronary angioplasty.

RECURRENT ISCHAEMIC EVENTS DURING EARLY FOLLOW UP

Follow up data are available for all 250 patients eight (range: three to 12) months after admission. Table 2 shows that during this period there were 45 recurrent ischaemic events: fatal reinfarction (17), non-fatal reinfarction (12), unstable angina (16). Also four patients died from progressive heart failure without a further acute ischaemic episode. An additional 10 patients underwent coronary artery bypass surgery either because of limiting angina or prognostically important three vessel disease, and five patients underwent coronary angioplasty for limiting angina. Thus there were a total of 64 cardiac events.

Other events excluded from analysis

Reinfarction occurred in three patients during Holter monitoring and in another three patients within 24 hours of completing it. Of these six events, two were fatal and four non-fatal. The recordings were abnormal in all cases, but none was included in the statistical analysis because the Holter changes were part of these acute events and did not predict them.

CHARACTERISTICS OF ST SHIFT ON HOLTER MONITORING

The 48 hour Holter recording was abnormal in 80 (32%) patients when only ST depression was taken into account, but was abnormal in 103 (41%) patients when ST elevation was included. Among those with an abnormal recording, the mean duration of ST shift (ST depression or ST elevation) was 75·8 (77·5) minutes, and exceeded one hour in 49 (20%) patients. The mean number of episodes of ST shift was 4·7 (4·1) and exceeded three episodes in 53 (21%) patients. Most episodes of ST shift were silent and only 5% were associated with chest pain.

HOLTER ST MONITORING AND RECURRENT ISCHAEMIC EVENTS

All events

There was a significant association between ST shift (ST depression or elevation) on Holter monitoring and recurrent ischaemic events (table 2). Thus, ST shift was present in 58% of patients who sustained an event compared with 37% of those who did not ($p \leqslant 0·01$) table 3). The relation was 58% sensitive and 63% specific for recurrent events with positive predictive accuracy of 36% and negative 81%. When analysis was confined to ST depression (ignoring ST

Table 3 Relation between Holter variables and all recurrent events

	Event (n = 64) n (%)	No event (n = 180) n (%)	χ^2 Value	p Value	Sensitivity	Specificity	Positive predictive accuracy	Negative predictive accuracy
Abnormal tape, ST depression or elevation (n = 103)	37 (58)	66 (37)	8·65	0·003	58	63	36	81
Abnormal tape, ST depression (n = 80)	29 (45)	51 (28)	6·18	0·013	45	72	36	79
Duration of ST shift, >60 min (n = 49)	21 (33)	28 (16)	8·76	0·003	33	84	43	78
More than three episodes of ST shift (n = 53)	21 (33)	32 (18)	6·28	0·02	33	82	40	78

elevation), the relation with recurrent events was less strong but remained statistically significant. A gradient of risk was identified depending on the cumulative duration of ST shift (depression or elevation). Thus, when the duration exceeded 60 minutes in 48 hours, specificity (84%) and positive predictive accuracy (43%) for recurrent events improved albeit with loss of sensitivity (33%). Similar results were found when the number of episodes of ST shift were taken into account, more than three episodes in 48 hours were highly specific (82%) for recurrent events.

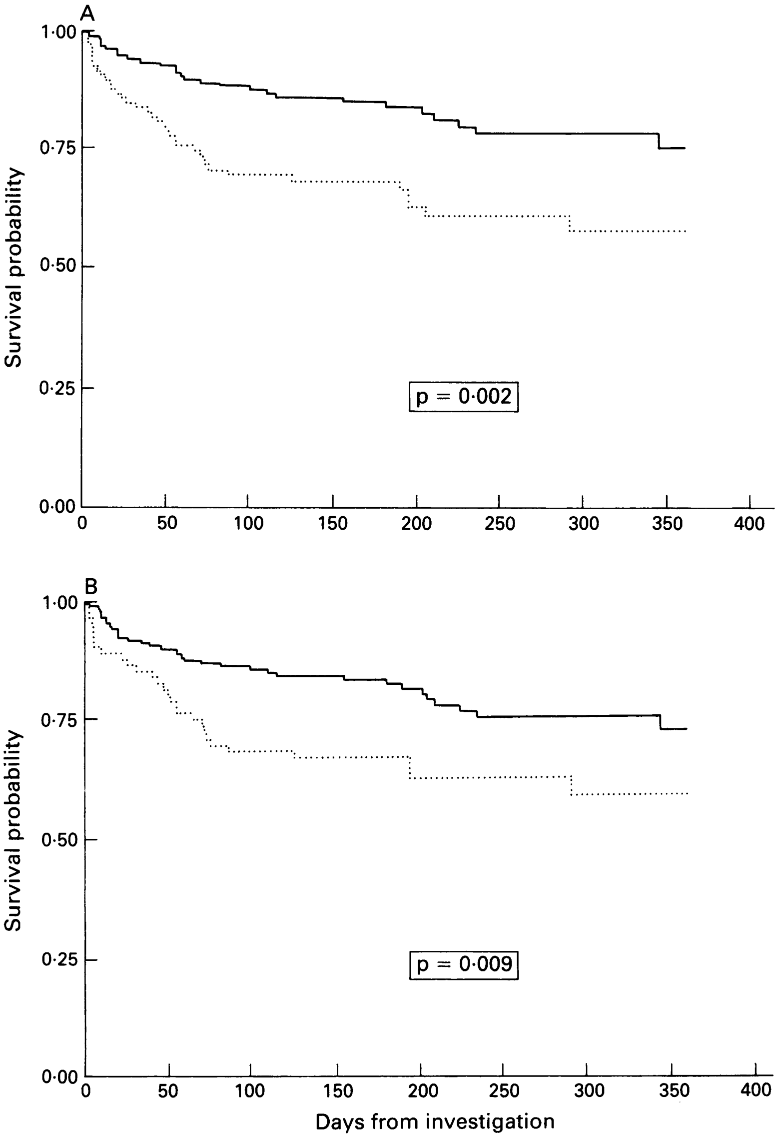

Figure 1 Kaplan-Meier event free survival curves (all events) comparing patients (A) with (broken line) and without (continuous line) ST shift (ST depression or elevation) on Holter monitoring, and (B) with (broken line) and without (continuous line) ST depression on Holter monitoring.

Analysis of event free survival confirmed a significant association between abnormal Holter recordings and recurrent ischaemic events, regardless of whether ST elevation was included in the analysis (fig 1). The Kaplan Meier curves show clearly that the period of greatest risk for patients with an abnormal Holter recording occurs in the early weeks after investigation when the risk of thrombotic reocclusion seems to be greatest.

Recurrent myocardial infarction

The association between an abnormal Holter recording and recurrent ischaemic events remained significant when the end point was restricted to fatal or non-fatal reinfarction (n = 29). Thus Holter ST shift was present in 69% of patients who sustained a further myocardial infarction compared with 39% of those who did not ($p \leqslant 0·01$ table 4). The relation was 69% sensitive and 61% specific for reinfarction with positive and negative predictive accuracies of 19% and 94%. When duration of ST shift ($\geqslant$60 minutes in 48 hours) or the number of ischaemic episodes (>3 in 48 hours) were taken into account, specificity improved (83% and 81%) but with loss of sensitivity (41% and 45%). A normal Holter recording was associated with a negative predictive accuracy for reinfarction exceeding 90%.

Analysis of event free survival confirmed a significant association between abnormal Holter recordings and recurrent ischaemic events, regardless of whether ST elevation was included in the analysis (fig 2). Again the Kaplan-Meier curves show that the period of greatest risk for patients with an abnormal Holter recording occurs early after investigation.

Early recurrent myocardial infarction

In 14 patients reinfarction occurred within 30 days of presentation (table 5). Holter ST shift was present in 79% of these patients compared with 40% of those without early reinfarction ($p \leqslant 0·01$). More than three episodes of ST shift were recorded in 57% of patients with early reinfarction compared with 20% of those without ($p \leqslant 0·001$). The relation between an abnormal Holter recording (ST depression or elevation) and early reinfarction was associated with 79% sensitivity and 60% specificity. Although positive predictive accuracy was low because of the small number of events, a normal Holter recording was associated with 98% negative predictive accuracy.

Table 4 Relation between Holter variables and reinfarction

	Event (n = 29) n (%)	*No event (n = 215) n (%)*	*χ^2 Value*	*p Value*	*Sensitivity*	*Specificity*	*Positive predictive accuracy*	*Negative predictive accuracy*
Abnormal tape, ST depression or elevation (n = 103)	20 (69)	83 (39)	9·66	0·002	69	61	19	94
Abnormal tape, ST depression (n = 80)	16 (55)	64 (30)	7·48	0·006	55	70	20	92
Duration of ST shift, >60 min (n = 49)	12 (41)	37 (17)	9·30	0·002	41	83	25	91
More than three episodes of ST shift (n = 53)	13 (45)	40 (19)	10·30	0·001	45	81	25	92

Discussion

The natural history of myocardial infarction has changed with the introduction of thrombolytic treatment. There is a lower mortality but an increased risk of recurrent thrombotic events.[1–8] The identification of those patients at risk remains an important management priority, but to date none of the currently available non-invasive tests has been shown to correlate with clinical outcome early after thrombolysis.[25] In this study, we have examined the diagnostic value of Holter ST segment monitoring 48 hours after thrombolysis, and have shown a significant association between ST segment shift and recurrent ischaemic events during six to 12 months of follow up. Although sensitivity was low when soft end points (unstable angina, need for revascularisation) were included in the analysis, it was appreciably higher for fatal and non-fatal reinfarction, particularly those events that occurred in the first 30 days.

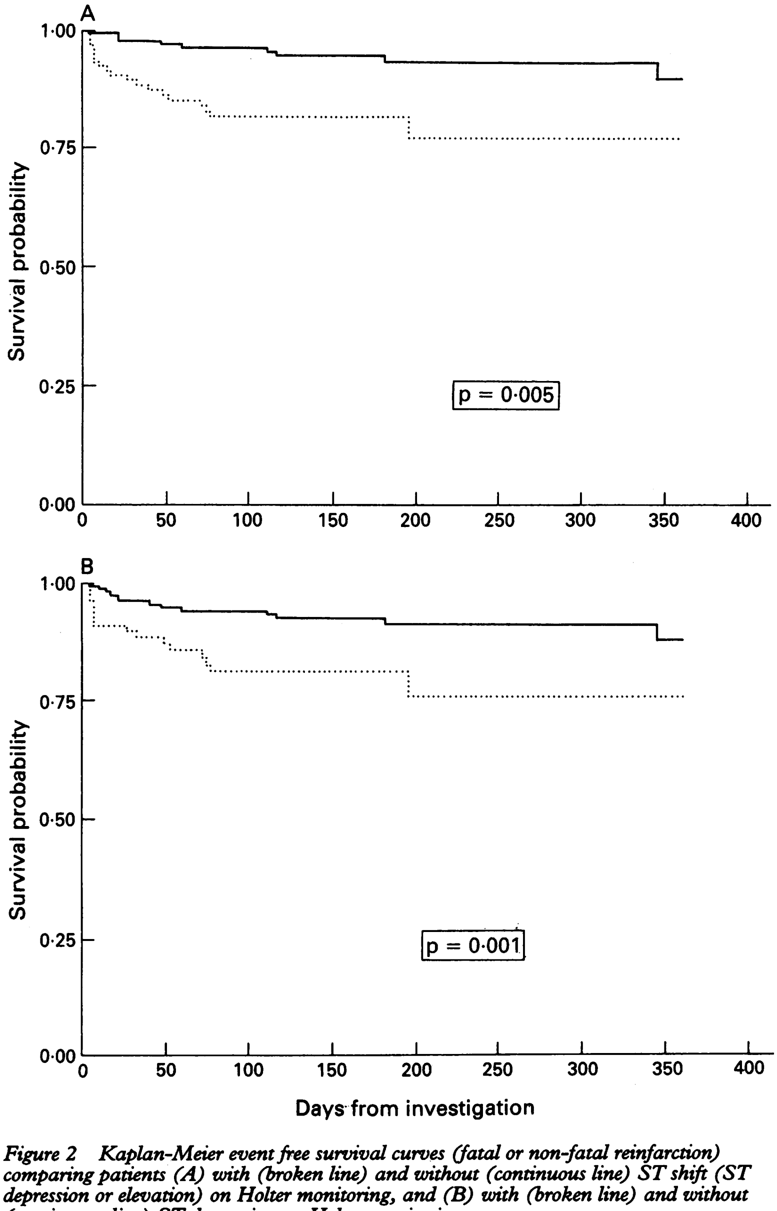

Figure 2 Kaplan-Meier event free survival curves (fatal or non-fatal reinfarction) comparing patients (A) with (broken line) and without (continuous line) ST shift (ST depression or elevation) on Holter monitoring, and (B) with (broken line) and without (continuous line) ST depression on Holter monitoring.

The presence of either ST depression or elevation identified 69% of the patients who sustained a recurrent myocardial infarction. The relative risk of reinfarction was increased with both total duration (ischaemic burden), and the number of episodes of ST shift, indicating a gradient of risk dependent on cumulative duration of electrocardiographic abnormality. The relation was strongest for identifying patients at risk of very early reinfarction (within 30 days), with an abnormal Holter recording providing 60% specificity and, importantly, 79% sensitivity. This high level of diagnostic sensitivity is particularly desirable for screening purposes and compares favourably with other non-invasive methods evaluated in the prethrombolytic era.[26–28] Nevertheless the positive predictive accuracy (11%) is low indicating that many patients screened would be subjected to unnecessary invasive investigation on the basis of a positive result. The negative predictive value (98%), on the other hand, is very high and a normal Holter recording clearly identifies a group of patients at very low risk.

Although ST depression on Holter ST monitoring has been associated with an adverse short[13–15] and long term[16] prognosis in patients with ustable angina, there is little information about its value in acute myocardial infarction. Those studies that are available have generally antedated the thrombolytic era, limiting their relevance to current therapeutic practice. Nevertheless, they have shown that abnormal Holter recordings may be predictive of an adverse prognosis in unselected patients with acute myocardial infarction,[17–19] and also in patients with low ejection fractions.[20] Other studies have been more difficult to interpret either because of few patients, and use of soft clinical end points,[21] or because of delays of up to 24 months before Holter recordings were obtained.[23] A retrospective case control study with data from the Beta Blocker Heart Attack Trial (BHAT) showed a significant association between ST shift on Holter monitoring and mortality among patients assigned placebo.[29] As in our study, there was

Table 5 Relation between Holter variables and early reinfarction (within 30 days)

	Event (n = 14) n (%)	No event (n = 230) n (%)	χ^2 Value	p Value	Sensitivity	Specificity	Positive predictive accuracy	Negative predictive accuracy
Abnormal tape, ST depression or elevation (n = 103)	11 (79)	92 (40)	8·05	0·005	79	60	11	98
Abnormal tape, ST depression (n = 80)	8 (57)	72 (31)	4·00	0·05	57	69	10	96
Duration of ST shift, >60 min (n = 49)	7 (50)	42 (18)	8·28	0·004	50	82	14	96
More than three episodes of ST shift (n = 53)	8 (57)	45 (20)	11·00	0·001	57	80	15	97

a gradient of risk according to the cumulative duration of ST shift; an ischaemic burden greater than 30 minutes being associated with a four fold relative risk. To date, however, only one other study (reported recently) has evaluated the role of Holter monitoring for risk stratification in patients with acute myocardial infarction treated by thrombolysis. Thus, Langer *et al* performed Holter ST monitoring (days 4 and 7), and radionuclide angiography (days 1 and 9) in 109 patients randomised to alteplase or placebo in the Tissue Plasminogen Activator: Toronto (TPAT) Study.[30] The principal findings were that patients with Holter ST depression (32%) had more severe stenosis in the infarct related artery and, by contrast with patients without ST depression, showed no improvement in left ventricular function between radionuclide studies. The effect was small, however, such that the mean ejection fraction at day 9 did not differ significantly between those with and without ST depression. There was no association between Holter ST depression and in hospital events, although these were few in number possibly reflecting patient selection and the relatively high incidence of early revascularisation. Long-term follow up data were only available in 76 patients but showed a greater frequency of death and reinfarction in patients with ST depression compared with those without (27% v 6%; $p < 0·03$). Numbers of patients were too small to allow a subgroup analysis confined to the thrombolysed group, and therefore the data are not directly comparable with our study. Nevertheless, the data provide a possible link between Holter ST depression, recurrent ischaemia as reflected by persistent left ventricular dysfunction, and an adverse prognosis. Two other studies have evaluated the role of continuous electrocardiographic monitoring during the early hours after thrombolytic treatment for acute myocardial infarction. Kwon *et al* studied 31 patients who presented within four hours of the onset of symptoms, and found a significant association between early recurrent ST segment elevation and coronary occlusion shown at coronary arteriography five to seven days later.[31] Similarly in a pilot study involving 21 patients, Dellborg *et al* found continuous QRS and ST segment vectorcardiographic monitoring to be predictive of coronary patency on early arteriography.[32] Both of these studies were limited in terms or numbers of patients and were therefore unable to relate electrocardiographic findings to clinical outcome.

In our study, the high proportion of silent ischaemic episodes during Holter monitoring after myocardial infarction accords with the findings of previous investigators[17 18 20 21] who have suggested that it may reflect activity of dynamic disease with periodic reductions in coronary supply rather than increased demand.[20 33 34] Successful thrombolytic treatment produces a potentially unstable lesion in the infarct related artery and exposes the patient to the risks of reocclusion.[9–11] Mechanisms of reocclusion remain unclear, but probably reflect a dynamic disease process that involves coronary vasoconstriction and platelet activation.[35 36] Thus the Holter ST shift identified in patients who later reinfarcted may reflect transient, subclinical episodes of total or subtotal coronary occlusion caused by the same dynamic mechanisms that lead eventually to sustained closure of the artery.

STUDY LIMITATIONS

The benefits of thrombolytic treatment are now so well established that it is now no longer possible to obtain properly controlled data. Thus it is not clear whether our conclusions about the potential role of Holter monitoring for risk assessment apply specifically to patients treated by thrombolysis. Other potential criticisms of our study relate to the timing of Holter monitoring and the diagnostic criteria for an abnormal recording. Although the baseline electrocardiogram is often abnormal during the first 24–48 hours, the ST segments have usually returned to baseline after two days, which allows reliable interpretation of the Holter recording.[21] As many recurrent events occur early after thrombolytic treatment,[37] the optimal time for Holter monitoring may prove to be within the first 48–96 hours, whereas ST monitoring was started a mean of 83 hours after infarction in our study. The incidence of ST shift in our study was comparable with that found by other investigators although the range of reported values is wide (15%–46%), probably reflecting differences in selection of patients time and duration of monitoring, number of electrocardiographic channels used, and criteria adopted for defining ischaemic episodes. It is generally accepted that ST depression on Holter monitoring indicates myocardial ischaemia in patients known to have coronary artery disease, but the importance of ST elevation remains unclear[38] and it has often been ignored in studies of this type.[18 22 23] Our own data have shown that inclusion of ST elevation of at least 0·2 mV as a criterion of abnormality contributes considerably to the prognostic value of Holter recording after thrombolytic treatment even though the mechanism is unknown. On empirical grounds, therefore, we would recommend that ST elevation be taken into account in Holter analysis for prognostic assessment after acute myocardial infarction treated by thrombolysis. Finally, cardiac medications were not routinely stopped before Holter monitoring, and it is unknown to what extent this may have influenced the results of the study.

CONCLUSIONS

There are relatively few data available regarding the role of Holter ST monitoring early after acute myocardial infarction particularly in patients treated by thrombolysis. The results of this study have shown that an abnormal Holter recording is associated with a heightened risk of recurrent events particularly within the first 30 days after thrombolysis when the risk of reocclusion is greatest. Importantly the patients were unselected, and included those unable to peform a predischarge treadmill stress test in whom the risk of recurrent ischaemic events is usually considered to be high. Holter monitoring may prove to have an important role in screening for patients likely to be at increased risk of early reinfarction after successful thrombolysis, although further evaluation is necessary before it can be recommended for use in routine clinical practice.

1 ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction:ISIS-2. *Lancet* 1988;**2**:349-60.
2 Simoons ML, Serruys PW, Brand M. Improved survival after early thrombolysis in acute myocardial infarction. *Lancet* 1985;**2**:578–82.
3 GISSI. Gruppo Italiano per to Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Long term effects of intravenous thrombolysis in acute myocardial infarction: final report of the GISSI study. *Lancet* 1987;**2**:871–5.
4 Simoons ML, Vos J, Tijssen JGP, *et al.* Long-term benefit of early thrombolytic therapy in patients with acute myocardial infarction: 5 year follow-up of a trial conducted by the Interuniversity Cardiology Institute of the Netherlands. *J Am Coll Cardiol* 1989;**14**:1609–15.
5 Feit F, Mueller HS, Braunwald E, *et al* and the TIMI research group. Thrombolysis in myocardial infarction (TIMI) phase 11 trial: outcome comparison of a "conservative strategy" in community versus tertiary hospitals. *J Am Coll Cardiol* 1990;**16**:1529–34.
6 SWIFT (should we intervene following thrombolysis?) Trial Study Group. SWIFT trial of delayed elective intervention v conservative treatment after thrombolysis with anistreplase in acute myocardial infarction. *BMJ* 1991;**302**:555–60.
7 AIMS Trial Study Group. Long-term effects of intravenous anistreplase in acute myocardial infarction: final report of the AIMS study. *Lancet* 1990;**335**:427–31.
8 Williams DO, Braunwald E, Knatterud G, *et al.* One year results of the Thrombolysis in Myocardial Infarction Investigation (TIMI) phase II trial. *Circulation* 1992;**85**:533–42.
9 Ellis SG, Topol EJ, George BS, *et al.* Recurrent ischaemia without warning: analysis of risk factors for in-hospital ischaemic events following successful thrombolysis with intravenous tissue plasminogen activator. *Circulation* 1989;**80**:1159–65.
10 Williams DO, Borer J, Braunwauld E, *et al.* Intravenous recombinant tissue-type plasminogen activator in patients with acute myocardial infarction: a report from the NHLBI thrombolysis in myocardial infarction trial. *Circulation* 1986;**73**:338–46.
11 Schroder R, Neuhaus K, Linderer T, Leizorovicz A, Wegscheider K, Tebbe U, for the ISAM study group. Risk of death from recurrent ischaemic events after intravenous streptokinase in acute myocardial infarction: results from the Intravenous Streptokinase in Myocardial Infarction (ISAM) Study. *Circulation* 1987;**76** (suppl 11):44–51.
12 Fox K. Silent ischaemia: clinical implications in 1988. *Br Heart J* 1988;**60**:363–6.
13 Gottlieb S, Weisfeldt M, Ouyang P, *et al.* Silent ischaemia as a marker for unfavourable outcomes in patients with unstable angina. *N Engl J Med* 1986;**314**:1214–9.
14 Larsson H, Jonasson T, Ringquist C, Fellenius L, Wallentin L. Diagnostic and prognostic importance of ST recording after an episode of unstable angina or non-Q wave myocardial infarction. *Eur Heart J* 1992;**13**:207–12.
15 Johnson SM, Mauritson DR, Winniford MD, *et al.* Continous electrocardiographic monitoring in patients with unstable angina pectoris: identification of high-risk subgroup with severe coronary disease, variant angina, and/or impaired early prognosis. *Am Heart J* 1982;**103**:4–12.
16 Gottlieb S, Weisfeldt M, Ouyang P, *et al.* Silent ischaemia predicts infarction and death during 2 year follow-up of unstable angina. *J Am Coll Cardiol* 1987;**10**:756-60.
17 Petretta M, Bonaduce D, Bianchl V, *et al.* Characterization and prognostic significance of silent myocardial ischaemia on predischarge electrocardiographic monitoring in unselected patients with myocardial infarction. *Am J Cardiol* 1992;**69**:579–83.
18 Bonaduce D, Petretta M, Lanzillo T, *et al.* Prevalence and prognostic significance of silent myocardial ischaemia detected by exercise test and continuous ECG monitoring after acute myocardial infarction. *Eur Heart J* 1991;**12**:186–93.
19 Currie P, Ashby D, Saltissi S. Prognostic value of ambulatory ST segment monitoring after acute myocardial infarction [abstract]. *Br Heart J* 1991;**66**:61.
20 Gottlieb S, Gottlieb S, Achuff S, *et al.* Silent ischaemia on Holter monitoring predicts mortality in high-risk post infarction patients. *JAMA* 1988;**259**:1030–41.
21 Ouyang P, Chandra N, Gottlieb S. Frequency and importance of silent myocardial ischaemia identified with ambulatory electrocardiographic monitoring in the early in-hospital period after acute myocardial infarction. *Am J Cardiol* 1990;**65**:267–70.
22 Tzivoni D, Gavish A, Zin D, *et al.* Prognostic significance of ischaemic episodes in patients with previous myocardial infarction. *Am J Cardiol* 1988;**62**:661–4.
23 Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. *Journal of the American Statistical Association* 1958;**53**:457.
24 Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemotherapy Reports* 1966;**50**:163.
25 Lavie CJ, Gibbons RJ, Zinsmeister AR, Gersh BJ. Interpreting results of exercise studies after acute myocardial infarction altered by thrombolytic therapy, coronary angioplasty or bypass. *Am J Cardiol* 1991;**67**:116–120.
26 De Belder MA, Pumphrey CW, Skehan JD, *et al.* Relative power of clinical, exercise test, and angiographic variables in predicting clinical outcome after myocardial infarction: the Newham and Tower Hamlets study. *Br Heart J* 1988;**60**:377–89.
27 Jespersen CM, Kassis E, Edeling CJ, Masden JK. The prognostic value of maximal exercise testing soon after first myocardial infarction. *Eur Heart J* 1985;**6**:769–72.
28 Fuller CM, Raizner AE, Verani MS, *et al.* Early post-myocardial infarction treadmill stress testing an accurate predictor of multivessel coronary artery disease and subsequent cardiac events. *Ann Internal Med* 1981;**94**:734–9.
29 Ruberman W, Crow R, Rosenberg CR, Rautaharju PM, Shore RE, Pasternack BS. Intermittent ST depression and mortality after myocardial infarction. *Circulation* 1992;**85**:1440–6.
30 Langer A, Minkowitz J, Dorian P, *et al.* Pathophysiology and prognostic significance of Holter-detected ST segment depression after myocardial infarction. *J Am Coll Cardiol* 1992;**20**:1313–7.
31 Kwon K, Freedman SB, Wilcox I, *et al.* The unstable ST segment early after thrombolysis for acute infarction and its usefulness as a marker of recurrent coronary occlusion. *Am J Cardiol* 1991;**67**:109–15.
32 Dellborg M, Topol EJ, Swedberg K. Dynamic QRS complex and ST segment vectorcardiographic monitoring can identify vessel patency in patients with acute myocardial infarction treated with reperfusion therapy. *Am Heart J* 1991;**122**:943–7.
33 Currie P, Saltissi S. Transient myocardial ischaemia after acute myocardial infarction. *Br Heart J* 1990; **64**:299–303.
34 Currie P, Saltissi S. Transient ischaemia after acute myocardial infarction: relationship to exercise ischaemia. *Eur Heart J* 1991;**12**:395–400.
35 Fitzgerald DJ, Catalla F, Roy L, Fitzgerald GA. Marked

platelet activation in vivo after streptokinase in patients with acute myocardial infarction. *Circulation* 1988; 77:142–50.
36 Harrison DG, Ferguson DW, Collins SM, *et al.* Rethrombosis after reperfusion with streptokinase: importance of geometry of residual lesions. *Circulation* 1984;**69**:991–9.
37 Ohman EM, Califf RM, Topol EJ, *et al*, and the TAMI study group. Consequences of reocclusion after successful reperfusion therapy in acute myocardial infarction. *Circulation* 1990;**82**:781–91.
38 Arnim T von, Hofling B, Schreiber M. Characteristics of episodes of ST elevation or ST depression during ambulatory monitoring in patients subsequently undergoing coronary arteriography. *Br Heart J* 1985; **54**:484–8.